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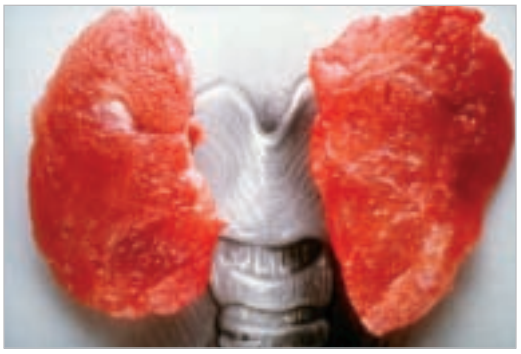
COMMUNIQUÉ

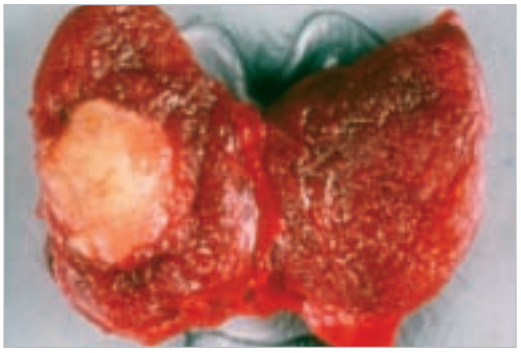
IMPROVING PATIENT CARE THROUGH ESOTERIC LABORATORY TESTING APRIL 2008

Laboratory Testing in Thyroid Cancer for Diagnosis and Follow-up—the Old and the New

In 2008, at least 32,000 new thyroid cancer cases will be diagnosed in the United States. Most of these patients will require long-term follow-up surveillance for tumor recurrence. Recent developments are changing some long-established patterns of thyroid cancer–related laboratory testing.



Enlarged thyroid gland due to Grave's disease.



Thyroid gland showing cancerous growth in right lobe.

Current Laboratory Testing in Thyroid Malignancies

Thyroglobulin (Tg) is the key tumor marker to detect recurrence of follicular cell–derived tumors, while calcitonin and carcinoembryonic antigen are used for the much rarer C-cell–derived medullary thyroid carcinoma (MTC). Stefan K. Grebe, MD, Division of Clinical Biochemistry and Immunology, Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester, says: "Tg measurements should always be interpreted in the context of simultaneous measurement of Tg autoantibodies (TgAB). TgAB occur in about 20% of thyroid cancer patients and can lead to falsely low Tg measurements." Bryan McIver, MBChB, PhD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, adds: "Although the presence of TgAB after thyroid surgery has

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been interpreted as an indicator of persis-tent thyroid cancer, there is uncertainty about the time course of TgAB decay in cured patients; the wide variability in detection sensitivity between different TgAB assays; and the cut-offs for normality in this setting. Thus, persistence of TgAB is a qualitative indicator of possible persistence of thyroid-derived tissue and should be interpreted with extreme caution."

New Developments in Tg Testing

Serum concentrations of Tg are highly specific for the presence of thyroid tissue in the body, but they are not specific for malignancy. The value of Tg measurement in thyroid cancer follow-up is therefore compromised in patients with more than a minimal amount of postsurgical thyroid tissue (remnant). Dr Grebe explains: "Each gram of thyroid remnant contributes approximately 1 ng/mL to serum Tg in patients with a detectable thyrotropin (TSH) level and 0.5 ng/mL in those with a suppressed serum TSH concentration. Consequently, many physicians recommend postsurgical radioiodine (RAI) remnant ablation to make Tg a better assessment tool to follow patients with thyroid cancer." Dr McIver adds: "However, low-risk patients following near-total thyroidectomy can have low levels of Tg—consistent with a small normal thyroid remnant—and might not require RAI ablation."

The success of RAI ablation has been traditionally assessed by diagnostic RAI scanning sometime after ablation, or by postablation stimulated Tg measurements—either after thyroid hormone withdrawal or, more commonly in recent years, after recombinant human TSH (rhTSH) administration. However, these unpleasant (thyroid hormone withdrawal) or costly (rhTSH) procedures may no longer be necessary. The newest-generation Tg assays—which have been available for the past 6 years and are used routinely at Mayo Clinic—have 4- to 10-fold better detection sensitivity than the older assays, obviating the need for stimulated Tg measurements in many cases. Our recent data suggest that a 4- to 8-week postablation unstimulated serum Tg concentration less than 0.1 ng/mL indicates complete remnant ablation. Similarly, we have recently demonstrated that unstimulated serum Tg levels less than 0.1 ng/mL during follow-up exclude thyroid cancer recurrence, except in patients with TgAB and in very rare individuals with highly dedifferentiated tumors.

One immediate practical benefit from this observation is that most patients with serum Tg level less than 0.1 ng/mL might not require fine needle aspiration (FNA) biopsy of enlarged neck nodes, unless these are deemed highly suspicious by experienced ultrasonographers. However, those patients with detectable serum Tg or TgAB should undergo FNA biopsy of most enlarged or questionable neck nodes. The FNA biopsy specimen is then examined by an experienced cytopathologist. While FNA biopsy is considered the diagnostic gold standard, it is not infallible, with the most common problem being nondiagnostic biopsies because of paucicellular or acellular aspirates. Christine L. H. Snozek, PhD, Division of Clinical Biochemistry and Immunology, Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester, says: "Tg measurement on needle washes can resolve many of these problem cases. Normal lymph nodes do not contain Tg, and therefore any detectable Tg in a node is highly suspicious for metastatic thyroid cancer. We have recently reviewed our experience with Tg measurements in 122 cases of lymph node FNA biopsies. We were able to provide a diagnosis in all 119 cases that also had cytology performed; cytopathology was nondiagnostic in 16 of these cases. The FNA biopsy Tg measurement with a cut-off of 1 ng/mL had a sensitivity of 100% and specificity of 96.2% (2 false positives). In the 103 cases with both diagnostic cytology and FNA biopsy Tg measurements, the results of both methods agreed in all but 5 cases; in 4 of these 5 cases, the final clinical and histopathologic diagnosis agreed with the FNA biopsy Tg measurement, rather than with the cyto-pathologic assessment."

Calcitonin Testing and Procalcitonin as an Alternative

Unlike Tg, which is used primarily for follow-up of patients with follicular cell–derived thyroid carcinomas, calcitonin plays a role in both initial diagnosis and follow-up of MTC. Its role in the initial diagnosis is based on the fact that baseline secretion of calcitonin by normal C cells is very low. However, a number of conditions other than MTC can lead to calcitonin elevations (Table). Thus, modest elevations (2- to 4-fold elevations above the upper limit of normal) in serum calcitonin concentrations often do not indicate the presence of a C-cell tumor. Other limitations of calcitonin assays include

- Variability between different assays—mandating that serial measurements on the same patient should, if possible, always be obtained with the same assay.
- Instability of the analyte—about 20% of a given amount of calcitonin will decay into fragments every 2 hours at room temperature or in a refrigerator. Samples for calcitonin measurements should be frozen immediately.

Calcitonin and its multiple decay fragments and precursor fragments interact in complex ways with the antibodies in calcitonin assays, making accurate quantification of very high calcitonin levels (eg, >800 pg/mL) difficult.

Dr Grebe explains: "For these reasons, we have recently started evaluating procalcitonin (PCT), a calcitonin precursor, as an alternative to calcitonin for diagnosis and follow-up of MTC patients. PCT is a much more stable analyte and does not seem to be affected by assay interference of calcitonin fragments. Our preliminary data show a good correlation between calcitonin and PCT levels in patients with suspected or confirmed MTC, as well as in normal individuals. If these data are confirmed, we may start recommending PCT as an analytically superior alternative to calcitonin in the near future."

Causes of Increased Serum Calcitonin Levels Unrelated to MTC

- Active autoimmune thyroiditis
- Hyperparathyroidism
- Lactation
- Mastocytosis
- Neonates
- Nonthyroid neuroendocrine neoplasms (eg, islet cell tumors, carcinoid tumors, small cell carcinomas of the lung) and (rarely) leukemias
- Renal failure
- Sepsis
- Severe noninfectious inflammatory conditions and massive trauma

Novel Molecular Tests

Dr McIver explains: "Detection of the tumorigenic BRAF V600E mutation is highly specific for papillary thyroid carcinoma, and we have recently shown that circulating tumor cells with this mutation can be detected in some patients with papillary thyroid cancer." Clinical validation studies are under way to determine how these observations can best be introduced into clinical practice to augment existing laboratory testing in thyroid cancer. We hope that this type of cancer-specific surveillance method might eliminate many of the uncertainties that currently complicate the interpretation of measurement of Tg and TgAB and simplify the management of patients with differentiated thyroid cancer."

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Graves' Disease in Children

Graves' disease accounts for 10% to 15% of all childhood thyroid disorders. Girls are 4 to 5 times more likely to be affected than boys. Aida N. Lteif, MD, of the Division of Pediatric Endocrinology and Metabolism, Department of Pediatric and Adolescent Medicine at Mayo Clinic in Rochester, says: "Typically the signs and symptoms of hyperthyroidism develop gradually. The symptoms may be subtle over several months before hyperthyroidism is diagnosed. Anxiety, hyperactivity, and declining school performance may be attributed to other causes, especially in adolescents. The main clinical manifestations, however, are comparable to those present in adults. Nocturia is also frequently reported in children. Fetal hyperthyroidism can result in intrauterine growth retardation, fetal tachycardia, and premature birth. Newborns with hyperthyroidism have poor weight gain, vomiting, diarrhea, and tachypnea, which may lead to heart failure. Craniosynostosis and mental retardation have been reported."

On physical examination, thyromegaly is present in more than 95% of children with Graves' disease. Ophthalmic findings are more common but less severe in children than in adults with Graves' disease—the findings include proptosis, lid lag, lid retraction, stare, chemosis, conjunctival injection, periorbital edema, excess lacrimation, pain, and diplopia. Pretibial myxedema is much more common in adults than in children. Bone age may be advanced, although final height does not appear to be affected. Costochondral calcifications may be present.

Laboratory Findings

In Graves' disease, circulating levels of thyroid hormones—thyroxine (T_4) and triiodothyronine (T_3)—are increased while thyroid-stimulating hormone (TSH) is suppressed. T_3 thyrotoxicosis—where primarily serum T_3 is increased—may be seen early in the course of the disease. Thyroid hormone receptor antibodies are usually increased at the time of diagnosis and can be measured by 2 types of assays:

- Receptor assays assess the capacity of Graves' immunoglobulins to inhibit labeled TSH from binding to thyroid membranes. Assay sensitivity is about 94% in children with untreated active Graves' disease.
- Bioassays assess the ability of immunoglobulin concentrates to stimulate the production of cyclic AMP from thyroid cells. Assay sensitivity is 73% to 91% in children with untreated active Graves' disease.

Peter J. Tebben, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition and Division of Pediatric Endocrinology and Metabolism at Mayo Clinic in Rochester, notes: "Untreated children with negative thyroid receptor antibodies usually have mild hyperthyroidism. The majority of patients in remission have negative findings with both thyroid receptor assays. Levels of thyroid-stimulating antibodies are typically higher in young patients with ophthalmopathy than in those without ophthalmopathy. Antibodies to thyroperoxidase are present in the majority of pediatric patients with Graves' disease."

Treatment

Treatment options for children with Graves' disease include antithyroid medications, thyroidectomy, or radioactive iodine (^{131}I). Children with moderate to severe symptoms often have symptomatic improvement if a β-adrenergic blocking agent, such as propranolol, is administered before initiation of specific therapy to reduce thyroid hormone concentrations. As with adults, no single therapy is appropriate for all patients. Although these options are the same as those available to adults with Graves' disease, ^{131}I is used considerably less often in children.

Antithyroid medications methimazole and propylthiouracil have been used extensively in children and are effective in the management of hyperthyroidism due to Graves' disease. Dr Lteif explains: "These drugs block the production of thyroid hormone, and propylthiouracil also inhibits the

conversion of T_4 to T_3. Although these medications are generally well tolerated, rash or gastrointestinal tract disturbance occasionally requires their discontinuation. Agranulocytosis and severe hepatic toxicity are rare yet serious adverse effects that need to be discussed with the child and the parents. Long-term remission after treatment with antithyroid medications occurs in fewer than 25% of children—the remission rate is even lower when TSH receptor antibody levels are exceedingly high."

Radioactive Iodine

The use of ^{131}I to treat Graves' disease in children was first reported about 50 years ago. Dr Tebben comments: "Despite many subsequent reports, the use of ^{131}I in children remains quite controversial. As with adults, a smaller dose of ^{131}I and a larger thyroid gland are predictive of recurrent or persistent hyperthyroidism after ^{131}I therapy. The short- and long-term safety data regarding ^{131}I use in children are reassuring and do not suggest a subsequent increased risk of thyroid malignancy or issues with fertility when compared with outcomes in children treated surgically or with medications. Also, progression of ophthalmopathy does not appear to be more frequent in children treated with ^{131}I. However, the available data are limited, and long-term follow-up is documented in relatively few children."

Surgery

Thyroidectomy is seldom chosen as definitive therapy for treatment of Graves' disease in adults. Geoffrey B. Thompson, MD, of the Department of Surgery at Mayo Clinic in Rochester, says: "In our practice, children undergoing definitive therapy for Graves' disease are treated with total or near-total thyroidectomy. Children are prepared preoperatively with antithyroid medications, β-adrenergic blockers, or both. Lugol's solution (saturated solution of potassium iodide) is added to the regimen approximately 10 days before surgery to reduce gland vascularity. Transient or permanent hypoparathyroidism and recurrent laryngeal nerve injury can result after thyroidectomy. Perioperative morbidity and mortality are low when the procedure is performed by an experienced surgeon. Our experience in 78 children treated with thyroidectomy between 1986 and 2003 resulted in no deaths, no permanent hypoparathyroidism, and no recurrent laryngeal nerve injury. Only 2 patients had recurrent hyperthyroidism—both having received bilateral subtotal thyroidectomies early on in the experience."

Summary

Graves' disease remains the most common cause of hyperthyroidism in children. No one treatment available is appropriate for every patient. A thorough discussion with the child and parents regarding the advantages and disadvantages of each treatment modality is essential to provide appropriate individualized treatment.

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Mayo Medical Laboratories offers a full array of testing for thyroid disease. For assistance in selecting the appropriate test for your patient, contact Mayo Laboratory Inquiry at 800-533-1710.

National Medical Laboratory Professionals Week

April 20-26, 2008

Laboratory Professionals: Delivering Today's Results for a Healthier Tomorrow

Since the development of the clinical laboratory science profession in the 1920s, this group has grown to approximately 300,000 practitioners. Without fanfare, these professionals have become key members of the health care team.

National Medical Laboratory Professionals Week was developed to:

- Recognize the vital contributions to health care made by those professionals engaged in clinical laboratory science in the United States.
- Acknowledge the professional dedication of the practitioners of clinical laboratory science to the health care consumer.
- Educate the public, government and private sectors about the key role played by the clinical laboratory professional.
- Enhance the image of clinical laboratory professionals in the public and private sectors.

Take time this week to acknowledge all that this group has provided to improve health care across the United States.

Test Update

Correction to "Serology Testing for *Strongyloides* and *Toxocara* Discontinued" (March 2008)

We regret that the March Communiqué announcement that *Toxocara canis* serology testing is no longer available because the reagents have been withdrawn in the US market included an error about the preferred test for this organism. Stool testing for ova and parasites is not useful for the diagnosis of *Toxocara canis* infection.

2008 Education Calendar

Upcoming Education Conferences . . .

Challenging Aspects of Phlebotomy
March 13–14, 2008
Mayo Clinic
Rochester, Minnesota

15th International Surgical Pathology Symposium
April 29–May 2, 2008
Divani Caravel Hotel
Athens, Greece

Bleeding and Thrombosing Diseases Wet Workshop
August 12, 2008
Kahler Hotel
Rochester, Minnesota

Bleeding and Thrombosing Diseases 2008 Mayo Update
August 13–15, 2008
Kahler Hotel
Rochester, Minnesota

Practical Surgical Pathology
September 11–13, 2008
Mayo Clinic
Rochester, Minnesota

Integration Through Community Laboratory Insourcing
October 1–3, 2008
Millennium Knickerbocker Hotel
Chicago, Illinois

Real-Time PCR for the Clinical Microbiology Laboratory
October 23-24, 2008
Mayo Clinic
Rochester, Minnesota

Continuous Process Improvement: Sharing our Lean Journey
November 6-7, 2008
Mayo Clinic
Rochester, Minnesota

Disease Management Strategies . . .

Vitamin D Testing
January 8, 2008
Presenter: Philip R. Fischer, MD

Endocrinology Testing
February 12, 2008
Presenter: Stefan K. Grebe, MD

HIV Update
March 4, 2008
Presenter: Zelalem Temesgen, MD

Pediatric Reference Ranges
April 15, 2008
Presenter: Piero Rinaldo, MD, PhD

Pediatric Diabetes
May 6, 2008
Presenter: Siobhan T. Pittock, MD

Vitamin D Deficiency: Bones and Beyond
August 5, 2008
Presenter: Kurt A. Kennel, MD

Rheumatoid Arthritis
September 9, 2008
Presenter: Clement J. Michet Jr., MD

Leukemias and Lymphomas
October 14, 2008
Presenter: William G. Morice II, MD, PhD

Alzheimer Update and Treatment
November 11, 2008
Presenters: Neill R. Graff-Radford, MD and Steven G. Younkin, MD

Cardiovascular Biomarkers—An Update
December 9, 2008
Presenter: Allan S. Jaffe, MD

FOR MORE INFORMATION contact Mayo Medical Laboratories Education Department at 800-533-1710 or visit us at MayoMedicalLaboratories.com/education

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MC2831-0408

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